

REVIEW ARTICLE

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The implications of signaling lipids in cancer metastasis

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Abstract

Metastasis is the most malignant stage of cancer. Lipid metabolic abnormalities are now increasingly recognized as characteristics of cancer cells. The accumulation of certain lipid species, such as signaling lipids, due to the avidity of lipid metabolism may be a causal factor of tumor malignant progression and metastatic behavior. In this review, we first describe signaling lipids implicated in cancer migration, invasion and metastasis. Next, we summarize the regulatory signaling hubs of lipid anabolic and catabolic metabolism. We then address lipid-rich circulating tumor cells (CTCs) and the lipid composition of exosomes budded off from tumor cells. We also present advances in targeting the regulatory hubs of lipid metabolism and signaling lipids in cancer therapy. Given the complexity of metabolic disorders in cancer, the development of significant portfolios of approaches to target signaling lipids by the integration of multiple chemical modulations, as well as molecular imaging modalities, should offer promising strategies for cancer therapy.

Introduction

Metabolic reprogramming is now acknowledged as a core hallmark of cancer, characterized by functional dependence on glucose and glutamine catabolic pathways. Tumors often share a common feature of uncontrolled cell proliferation; therefore, they must efficiently produce biomass components and energy for expansion and further dissemination^{1–4}.

Lipid metabolic abnormalities are now increasingly recognized as a signature of cancer cells^{5–7}. Highly proliferative cancer cells show enhanced lipid avidity by either increasing the uptake of exogenous lipids and lipoproteins or upregulating *de novo* lipid synthesis⁵. Activation of a variety of oncogenic pathways deregulates lipid metabolic processes, leading to the accumulation of certain lipid species such as signaling lipids. These bioactive lipids can serve as secondary signaling messengers to coordinate

signal transduction cascades and to modulate a variety of carcinogenic processes, including cell proliferation, survival, chemoresistance and metastatic formation. Moreover, in the tumor microenvironment, noncancerous cells, such as endothelial cells, inflammatory cells, immune cells, fibroblasts and adipocytes, also play crucial roles in tumor expansion and malignant progression. Lipid autacoids, which are mainly composed of signaling lipids, can potentially target different cellular components in tumor microenvironments and conduct intercellular communication between cancerous and noncancerous cells⁸.

Tumor metastasis remains the major cause of cancer-related mortality, highlighting the importance of exploring new strategies to prevent and control tumor metastasis⁹. Current research on metabolism has been mostly focused on the primary tumor, while metabolic adjustments during each step of metastasis have received less attention¹⁰. In this review, we first discuss signaling lipids implicated in cancer migration, invasion and metastasis. Next, we summarize the regulatory hubs of anabolic and catabolic lipid metabolism. We address lipid-rich CTCs and the lipid composition of exosomes budded off from tumor cells. We also present advances in targeting the

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regulatory hubs of lipid metabolism and signaling lipids in cancer therapy (Table 1)^{11–27}.

Signaling lipids associated with cancer metastasis

In cancer cells driven by oncogenic signaling or genetic mutation of critical metabolic enzymes, the balance of metabolite homeostasis is disrupted²⁸. Accumulation of signaling lipids, including eicosanoids, phosphoinositides, sphingolipids, and fatty acids, alters the cellular biochemical foundation and might be a causal factor of tumor malignant progression and metastasis^{29–33} (Fig. 1).

Eicosanoids

Arachidonic acids are metabolized through the cyclooxygenase, lipoxygenase (LOX) and P450 epoxygenase (EPOX) pathways to generate eicosanoids, which include prostanoids, leukotrienes, hydroxyeicosatetraenoic acids, epoxyeicosatrienoic acids (EETs) and hydroperoxyeicosatetraenoic acids^{34,35}. Since prostanoids, such as the proinflammatory

PGE₂, have long been documented for their prominent role in promoting tumor growth and metastasis^{20,35–42}, we will focus on the leukotrienes and EET species of eicosanoids in this review.

Leukotrienes (LTs)

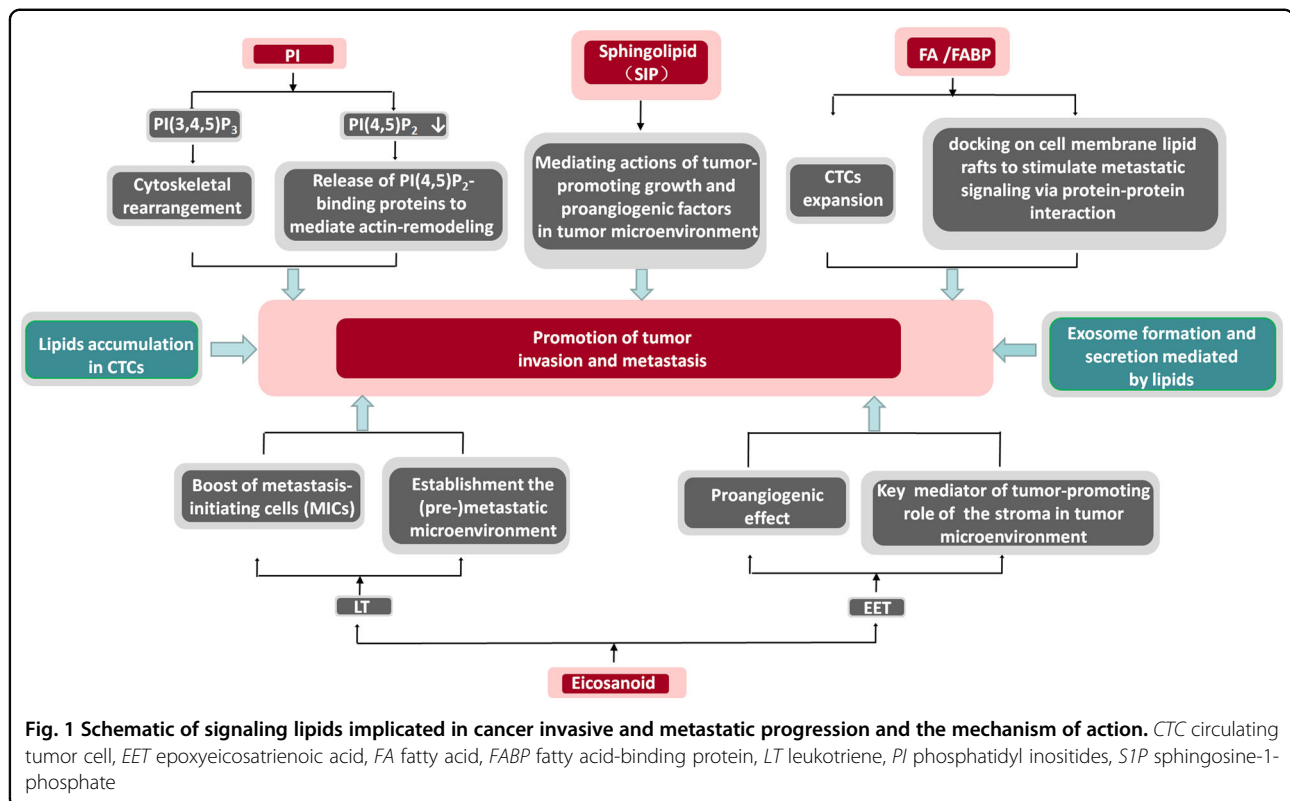
LTs are generated by Alox5 (arachidonate 5-lipoxygenase) and are primarily produced in stimulated leukocytes. Although in comparison to prostanoids, much less is known about the involvement of proinflammatory LTs in tumor progression, emerging evidence suggests that LTs might have an important role in the establishment of premetastatic microenvironments.

Wculek et al. reported that neutrophil-derived LTs selectively expand the subpool of breast cancer cells with high tumorigenic potential and aid the colonization in a secondary organ site¹⁷. LTs, mainly leukotriene B₄ and the cysteinyl leukotrienes C₄, D₄ and E₄ (LTC₄/D₄/E₄), boosted the heterogeneity of cancer cells, favoring

Table 1 Pharmacological tools to manipulate oncogenic regulatory pathways and lipid mediators associated with cancer metastasis

Category	Target	Compound	Mechanism	References	
Regulatory pathways of signaling lipid metabolism	ACC	Soraphen A	ACC inhibitor	Beckers et al. 2007 [11]	
	AMPK	Metformin	Activates AMPK, FDA approved	Pollak 2012 [12]	
	PI3K	GDC-0326	p110α PI3K inhibitor	Soler A et al. 2016 [13]	
	PI3K/mTOR	NVP-BEZ235	PI3K inhibitor mTOR inhibitor	Xie G et al. 2017 [14]	
Signaling lipids	SREBP	Fatostatin	SCAP inhibitor	Kamisuki S et al. 2009 [15]	
	FABPs	FABP4	Carbazole butanoic acid	FABP4 inhibitor	Wang YT et al. 2016 [16]
			Aryl sulfonamide	FABP4 inhibitor	Wang YT et al. 2016 [16]
Leukotrienes	FABP5	Pyrazole	FABP5 inhibitor	Wang YT et al. 2016 [16]	
	Alox5	zileuton	Alox5 inhibitor, LT↓	Wculek SK et al. 2015 [17]	
Prostaglandin	LOX	NDGA	LOX ↓	Koontongkaew et al. 2010 [18]	
	COX-2	Indomethacin	COX-2↓	Galfi et al. 2005 [19]	
		Celecoxib	COX-2↓	Wang D et al. 2015 [20]	
	PGD2	15-dPGJ 2	Akt ↓, PPARγ ↑	Shin et al. 2009 [21]	
		PGJ2 /15-dPGJ2	PPARγ ↑	Chinery et al. 1999 [22]	
	PGE2	ONO-AE3-208	EP4 ↓	Yang et al. 2006 [23]	
		Curcumin	PGE 2 ↓	Lev-Ari et al. 2005 [24]	
Sphingolipids		Fish oil	PGE 2 ↓	Mund et al. 2007 [25]	
		EPA	PGE 2 ↓	Petrik et al. 2000 [26]	
	PGI2	Olive oil	6-keto PGF 1α ↓	Petrik et al. 2000 [26]	
	SPHK1	FTY720	SPHK1 inhibitor, S1P↓	Patmanathan SN et al. 2016 [27]	

ACC, acetyl-CoA carboxylases; Alox5, arachidonate 5-lipoxygenase; AMPK, AMP-activated protein kinase; COX, cyclooxygenase; FABPs, fatty acid-binding proteins; LOX, lipoxygenase; mTOR, mammalian target of rapamycin; PG, prostaglandin; PI3K, phosphoinositide 3-kinase; SREBP, sterol regulatory element-binding proteins; SPHK1, sphingosine kinases



metastasis-initiating cells (MICs, the $CD24^+CD90^+$ population), and led to increased metastatic competence of total breast cancer cells. Moreover, cells expressing LT receptors were shown to be enriched among MICs. Pharmacological inhibition of LOX5 by zileuton blocked LT production and impaired neutrophil prometastatic activity; consequently, there was reduced human breast cancer progression to the lungs. Additionally, selective inhibition of LOXs with NDGA (nordihydroguaiaretic acid) in colorectal cancer cells also decreased the invasive capacity of the cells via inhibition of the activities of the matrix metalloproteinases MMP-2 and MMP-9¹⁸. Considering that leukocytes can act as the main component and driver of metastatic establishment within the pre-metastatic niche in a LT/LOX5-dependent fashion, targeting the noncancer-cell component of tumor microenvironments, as well as the lipid-metabolizing enzymes and proinflammatory signaling lipids, might offer novel therapeutic approaches to limit cancer metastatic progression.

Epoxyeicosatrienoic acids (EETs)

Arachidonic acid production is catalyzed by cytochrome P450 (CYP) epoxygenase to generate EETs, which include four regioisomeric epoxyeicosatrienoic acids, 5,6-EET, 8,9-EET, 11,12-EET and 14,15-EET. EETs are mainly secreted by endothelial cells and are metabolized by soluble epoxide

hydrolase (sEH)^{43,44}. Although EET receptors have not been fully identified, multiple pathways, including the GPCR/PPAR/RXR, VEGF, EGFR, tumor necrosis factor α (TNF α) and matrix metalloproteinase (MMP) pathways, are involved in the mechanism through which EETs stimulate tumor growth, angiogenesis and metastasis^{45–47}.

Elevated EET levels in multiple tumor types are associated with aggressive and metastatic cell behavior. In breast cancer, upregulation of epoxygenase CYP2C8, 2C9, and 2J2 and low expression of sEH were reported to account for EET augmentation⁴⁸. Panigrahy et al. demonstrated that in a variety of transplantable and genetically engineered mouse tumor models, endothelium-derived and systemic 14,15-EET triggered spontaneous multiorgan metastasis and escape from tumor dormancy. Downregulation of sEH resulted in increased EET levels, which subsequently stimulated the secretion of VEGF by the endothelium. Thus, the elevation of EET levels in endothelial cells at the metastatic site, and not the excessive growth of the primary tumor, led to tumor-associated angiogenesis and metastasis⁴⁹.

Altogether, EETs can act as key mediators of protumorigenic role of the stroma in the tumor microenvironments, mainly via their proangiogenic effects. Therefore, inhibitors of EET bioactivity, such as EET antagonists, inhibitors of endothelial epoxygenases, or the overexpression of sEH may represent new intervention

strategies for the metastatic progression of angiogenic cancers.

Phosphoinositides

Abundant alteration of phosphatidyl inositides (PIs) in membranes represents a feature of cancer. PIs serve as major determinants of membrane identity and function as membrane trafficking regulators^{50–53}. Among others, PI(3,4,5)P₃ and PI(4,5)P₂ are closely implicated in tumor cell migration and metastasis. They regulate cellular processes by recruiting, activating or inhibiting proteins at the plasma membrane to impact actin dynamics, thus causing alterations in cellular migration and metastatic capacity.

Phosphoinositide 3-kinase (PI3K) catalyzes the production of phosphatidylinositol-3,4,5-trisphosphate (PI[3,4,5]P₃) from its precursor PI(4,5)P₂. Elevation of PI(3,4,5)P₃ levels directs the guanine nucleotide exchange factors for Rho GTPases (such as Vav and Tiam) to the cell membrane, and the subsequent cytoskeletal rearrangements enhance cell migration and metastasis⁵⁴. However, in breast cancer cells, reduced PI(4,5)P₂ abundance in the plasma membrane enhances cellular migration and metastatic capacity. Senglaub et al. reported that PTPRN2 and PLCβ1 enzymatically reduced plasma membrane PI(4,5)P₂ levels, which resulted in the release of the PI(4,5)P₂-binding protein cofilin from its inactive, membrane-sequestered state, allowing it to enter the cytoplasm. Consequently, cofilin mediated actin-remodeling and enhanced cellular migration and metastasis⁵¹.

Several drugs, such as NVP-BEZ235, targeting the PI3K pathway are currently undergoing phase II and III clinical trials in patients with advanced disease^{13,14,55,56}. NVP-BEZ235 effectively inhibited cell migration and metastasis *in vitro* and *in vivo*, and combinations with vincristine potentiated its antimetastatic effects⁵⁶. Since tumors with constitutively elevated PI(3,4,5)P₃ are especially sensitive to the mTORC1 inhibitor rapamycin^{55,56}, PIs such as PI(3,4,5)P₃ may be exploited as biomarkers to identify PI3K-dependent cancers that are more likely to respond to drugs targeting PI3K/mTOR signaling.

Sphingolipids

Sphingolipid metabolites, such as ceramide and sphingosine, act as important modulators of cell survival, angiogenesis, migration and metastasis^{27,57–59}. Sphingosine-1-phosphate (S1P) is a bioactive lipid produced by the sphingosine kinases SPHK1 and SPHK2, and it can be dephosphorylated by sphingosine phosphatase or irreversibly degraded by S1P lyase (SGPL1)⁶⁰. S1P exerts its effect via autocrine or paracrine signaling, mostly mediated by a family of five cell surface G protein-coupled receptors termed S1PR1–5^{61–63}. Moreover, S1P can bind intracellular targets such as HDAC1/2 (histone deacetylases 1/2) and NF-κB⁶¹.

Patmanathan et al. demonstrated that overexpression of SPHK1 and low levels of SGPL1 accounted for the augmentation of S1P levels in oral squamous cell carcinoma (OSCC). S1P protected OSCC cells from cisplatin-induced death and enhance their migration and invasion. Moreover, S1PR1 was shown to be closely associated with persistent activation of signal transducer and activator of transcription-3 (STAT3) and IL-6 expression in both tumor cells and the tumor microenvironment, both of which contributed to tumor malignant progression and distant dissemination⁶⁴. Notably, FTY720 (2-amino-2-[2-(4-octylphenyl)]-1,3-propanediol hydrochloride), an inhibitor of SPHK1, can inhibit the proliferation and migration of a variety of cancer cell lines and suppresses tumor growth, angiogenesis and metastasis *in vivo*²⁷.

Because S1P not only affects tumor cells but also mediates the actions of tumor-promoting growth and proangiogenic factors in the tumor microenvironment, it may be developed into a bona fide cancer target.

Fatty acids (FAs) and lipid-binding proteins

Excessive incorporation of FAs into cancer cell membranes results in membrane phase separation, reduced cell-cell contact, and enhanced surface adhesion and tissue invasion^{31–33}. Le et al. used an animal cancer model to show that mice with excess plasma FFAs due to a high fat diet (HD) exhibited early appearance of a high number of CTCs and increased lung metastasis³¹. Abundant polyunsaturated FFAs in the blood plasma induced cancer cell membrane phase separation and the polarized distribution of cellular content; these exposed cells strongly resembled CTCs isolated from HD-fed mice.

Fatty acid-binding proteins (FABPs) are a family of low molecular-mass intracellular lipid-binding proteins consisting of ten isoforms, FABP1–10. FABPs are involved in binding and storing FAs, as well as transporting them to the appropriate compartments in the cell, including the plasma membrane, nucleus, endoplasmic reticulum, mitochondria and peroxisomes⁶⁵.

Lipids can serve as passive components of cell membranes, in which they form lipid rafts that facilitate signaling protein recruitment and protein-protein interactions to activate signal transduction pathways. Hence, FABPs, acting as chaperonins of lipids, might stimulate metastasis-associated signaling through protein-protein interactions after docking on membrane rafts. Liver fatty acid-binding protein (L-FABP) uniquely binds to ligands (e.g., long chain fatty acids) and hydrophobic molecules (e.g., cholesterol and bile acids). Ku et al. reported that L-FABP interacted with VEGFR2 on membrane rafts and subsequently activated the downstream AKT/mTOR/P70S6K/4EBP1 and Src/FAK/cdc42 pathways. This activation resulted in upregulation of VEGF-A, accompanied by an increase in both the

angiogenic potential and the migration activity of hepatocellular carcinoma cells⁶⁶. Moreover, several FABP isoforms are strongly implicated in cancer metastatic progression. High expression of FABP3 or FABP4 in non-small cell lung cancer (NSCLC) was significantly associated with advanced tumor node metastasis stage and had a negative impact on the overall survival of NSCLC patients⁶⁷. FABP5 increased the metastasis of triple negative breast cancer in part by inhibiting EGFR proteasomal degradation and EGF-induced metastatic signaling⁶⁸. In addition, FABP7 is involved in fatty acid metabolism and might be developed into a useful marker for the detection of metastatic melanoma⁶⁹.

Overall, FABPs represent potential targets in cancer therapy, and FABP inhibitors could be promising cancer treatments that inhibit or reduce early-stage tumors and metastasis¹⁶.

Regulation of signaling lipid metabolism

Metabolite homeostasis is determined by the associated metabolic pathways that synthesize or degrade metabolites. Among others, SREBP signaling, PI3K/AKT/mTORC, AMPK/ACC, SIRT1/PGC1 α axes and their reciprocal dialogs serve as the regulatory hubs of signaling lipid metabolism (Fig. 2).

SREBP signaling

Most enzymes involved in fatty acid and cholesterol biosynthesis are regulated by the sterol regulatory

element-binding proteins (SREBPs), which are transcription factors in the helix-loop-helix leucine zipper family. Three SREBP isoforms, SREBP1a, SREBP1c and SREBP2, have been identified in mammalian cells. SREBP1 mainly regulates fatty acid, phospholipid and triacylglycerol synthesis, while SREBP2 controls the expression of cholesterol-synthesis genes⁷⁰. SREBP function is modulated by protein posttranslational modifications. AMPK directly phosphorylates SREBP to prevent its proteolytic activation^{71,72}. SREBP can also be phosphorylated by glycogen synthase kinase 3, resulting in protein polyubiquitination and degradation⁷³.

Due to the importance of SREBP activation in signaling lipid anabolic metabolism, its overexpression is significantly associated with aggressive pathological features and has prognostic roles in multiple types of human cancer^{74–78}. Genetic silencing of SREBP-2 inhibited prostate cancer (PCa) cell growth, stemness, and xenograft tumor growth and metastasis⁷⁸. Genetic overexpression of SREBP-1 in PCa cells resulted in increased fatty acid synthase and NADPH oxidase 5 (Nox5) expression, ROS generation, fatty acid and lipid droplet accumulation. These alterations induced by SREBP-1 promoted the growth, migration, and invasion progression of PCa cells in vitro and in vivo⁷⁴. Fatostatin was recently discovered as a specific inhibitor of SCAP (SREBP cleavage-activating protein), which is required for SREBP activation¹⁵. It may be developed into a novel strategy targeting lipogenesis and cholesterologenesis to

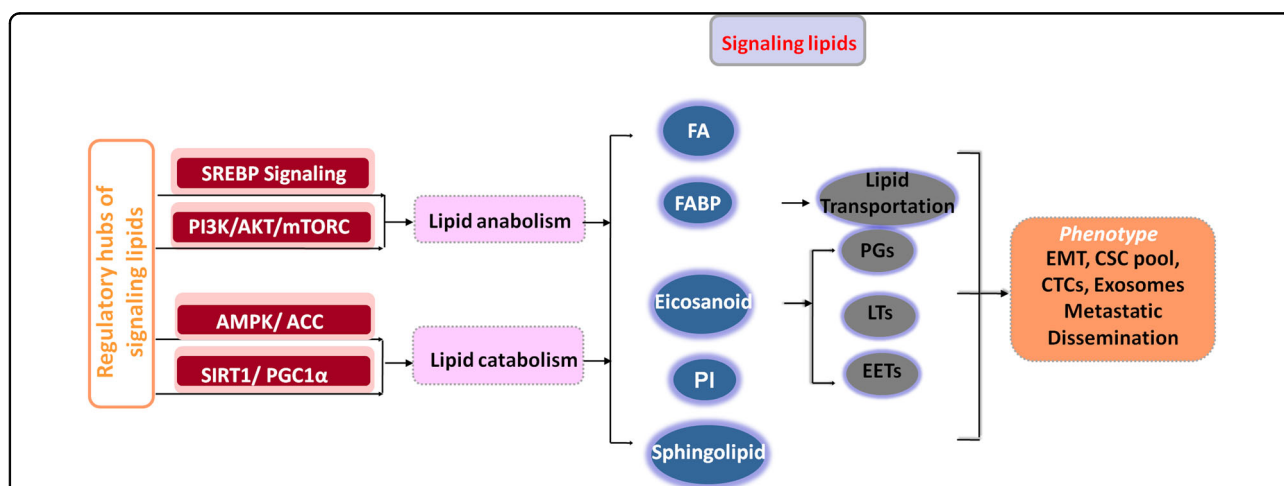


Fig. 2 Connections among lipid regulatory pathways, signaling lipids and the invasive and metastatic phenotypes of tumor cells. SREBP signaling and the PI3K/AKT/mTORC axis are mainly responsible for lipid anabolic metabolism, and the AMPK/ACC and SIRT1/PGC1 α axes contribute to lipid catabolic metabolism in tumor cells. Accumulating signaling lipids, such as FAs, eicosanoids, PIs, sphingolipids and FABPs, represent causal factors for the cancer cell EMT program, the maintenance of the CSC subpool, the increased number of CTCs and the metastatic phenotype. CSC cancer stem cell, CTC circulating tumor cell, EETs epoxyeicosatrienoic acids, EMT epithelial–mesenchymal transition, FAs fatty acids, FABPs fatty acid-binding proteins, LTs leukotrienes, PGs prostaglandins, PIs phosphatidyl inositides, ACC acetyl-CoA carboxylases, Alox5 arachidonate 5-lipoxygenase, AMPK AMP-activated protein kinase, COX cyclooxygenase, FABPs fatty acid-binding proteins, LOX lipoxygenase, mTOR mammalian target of rapamycin, PG prostaglandin, PI3K phosphoinositide 3-kinase, SREBP sterol regulatory element-binding proteins, SPHK1 sphingosine kinases

treat aggressive types of cancer that have elevated lipid accumulation, undergo rapid proliferation and often develop resistance to current anticancer therapies⁷⁹.

PI3K/AKT/mTORC axis

The PI3K/AKT/mTORC (phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin complex) axis impinges on various aspects of metabolism and impact on signaling lipid anabolic metabolism^{80,81}. PI3Ks (type I) are activated by cell surface receptors and subsequently transduce the inputs into the accumulation of the signaling lipid PI(3,4,5)P₃, which then facilitates the activation of many effectors, including the serine/threonine kinase AKT. AKT can phosphorylate ATP-citrate lyase and activate the expression of several genes involved in cholesterol and fatty acid biosynthesis⁸⁰. SREBP is an important component of the metabolic regulatory network downstream of the PI3K/AKT/mTORC axis. Both AKT2 and mTORC1 activities have been found to be required for the induction of SREBP1c and for lipid synthesis in the liver^{82,83}. In addition, the PI3K/AKT axis is implicated in the transportation and function of signaling lipids. PI3K/Akt signaling mediates the phosphorylation of the signaling lipid S1P transporter, Spns2 (spinster homolog 2), by hepatocyte growth factor and lamellipodia formation in lung endothelium cells⁸⁴.

AMPK /ACC axis

The AMPK/ACC axis has been proposed as a key contributor to lipid homeostasis. AMP-activated protein kinase (AMPK) is a heterotrimeric serine/threonine kinase that is activated under conditions of cellular energy shortage. Once activated, AMPK redirects lipid metabolism towards increased catabolic fatty acid oxidation and decreased anabolic lipid synthesis through the phosphorylation of acetyl-CoA carboxylases (ACCs)⁸⁵. ACCs are responsible for the carboxylation of acetyl-CoA to form malonyl-CoA, which represents the first step in de novo lipid synthesis. In addition to ACCs, other key enzymes of lipid metabolism are known substrates of AMPK, such as Desnutrin/ATGL, whose phosphorylation facilitates the lipolytic program^{86–90}. Given the important roles of the AMPK/ACC axis in the regulation of fatty acid synthesis, activation of AMPK or inhibition of ACC may develop into attractive therapeutic options in cancer types associated with fatty acid accumulation^{12,85,91,92}.

SIRT1/PGC1 α axis

Sirtuins in mammals share extensive homology with the Sirt2 gene in yeast and comprise a small family with seven members, SIRT1–SIRT7. SIRT1 is the most well-characterized member of the sirtuin family and can deacetylate histone and nonhistone proteins. Through its ability to deacetylate target proteins, SIRT1 regulates lipid

metabolism by interacting with certain partners such as peroxisome proliferator-activated receptor gamma coactivator-1 α (PGC-1 α), SREBP, PPAR γ (peroxisome proliferator-activated receptor gamma), LXR (liver X receptor), Akt and AMPK in a cell context-dependent manner^{35,93–96}.

The deacetylation of PGC-1 α by Sirt1 has been extensively implicated in the metabolic control of signaling lipid homeostasis^{93–95}. PGC-1 α acts as a master transcriptional regulator of mitochondrial biogenesis, lipogenesis and fatty acid oxidation⁹⁷. In fasting liver, the SIRT1/PGC-1 α axis was activated to initiate transcription of fatty acid oxidation genes and to promote fatty acid expenditure⁹³. Considering that SIRT1 and/or PGC-1 α expression is highly associated with tumor invasion and metastasis^{98–100}, the SIRT1/PGC-1 α axis may provide an important molecular link that couples lipid metabolism to tumor malignant progression.

Lipids implicated in CTCs

As the shedding of cells from the primary tumor into peripheral blood is a necessary step in tumor dissemination, CTCs are considered promising prognostic metastatic biomarkers⁶⁹. Accumulating evidence supports the idea that CTCs contain a subpopulation of cancer stem cells that give rise to distant metastases¹⁰¹. Intracellular lipid content might serve as a potential biomarker of CTCs.

Coherent anti-Stokes Raman scattering (CARS) microscopy is a highly sensitive imaging technique for the visualization of lipid-rich structures. Metastatic human prostate cancer cells display rapid lipid uptake and slow lipid mobilization kinetics when incubated with human plasma spiked with palmitic acid³². CTCs isolated from multiple types of metastatic cancer patients exhibited strong CARS signals due to intracellular lipid accumulation³¹. Thus, in addition to the routine strategies for CTC detection, such as capturing CTCs by microposts or magnetic beads coated with specific antibodies¹⁰¹, measuring DNA shedding by CTCs¹⁰², and physical separation by size and density¹⁰³, the detection of lipid-rich CTCs with label-free and nonperturbative imaging using CARS microscopy or other multimodal imaging systems may be developed as effective clinical modalities.

Lipids in exosomes

Exosomes are small vesicular bodies (40–150 nm in diameter) released by the exocytosis of multivesicular bodies (MVBs)^{104,105}. Exosomes that bud off from tumor cells might help stromal cells modulate the micro-environment and prime organs for cancer spread¹⁰⁶. Lipids can mediate the formation and secretion of exosomes and contribute to their role in tumor growth and dissemination. Moreover, the composition and content of

lipid species enriched in exosomes may be potential sources of noninvasive cancer biomarkers.

Several lipids and lipid-metabolizing enzymes have been shown to participate in the production and release of exosomes¹⁰⁷. Among others, the levels or formation of phosphoinositides, diacylglycerol, phosphatidic acid (PA), as well as ceramide, have important roles in this process^{108–110}. In prostate cancer PC-3 cells, impaired PI(3,5)P2 production by knockdown of PIKfyve or inhibition of enzyme activity increased exosome secretion and inhibited the fusion of MVB with lysosomes, which might be attributed to the ability of PI(3,5)P2 to act as an agonist of the lysosomal Ca²⁺ channel TRPML1¹¹¹. Trajokovic et al. observed that neutral sphingomyelinase (nSMase) promotes the secretion of exosomes from Oli-neu cells triggered by ceramide formation¹⁰⁹. Moreover, the regulatory mechanisms are different not only among various cell types but also among various exosome populations within a single cell line¹⁰⁷. In breast cancer MCF-7 cells, the enzyme phospholipase D2 (PLD2) was required for the formation of intraluminal vesicles within a fraction of the MVBs, while inhibition of PLD2 activity attenuated only the secretion of syntenin-containing exosomes in these cells¹⁰⁸.

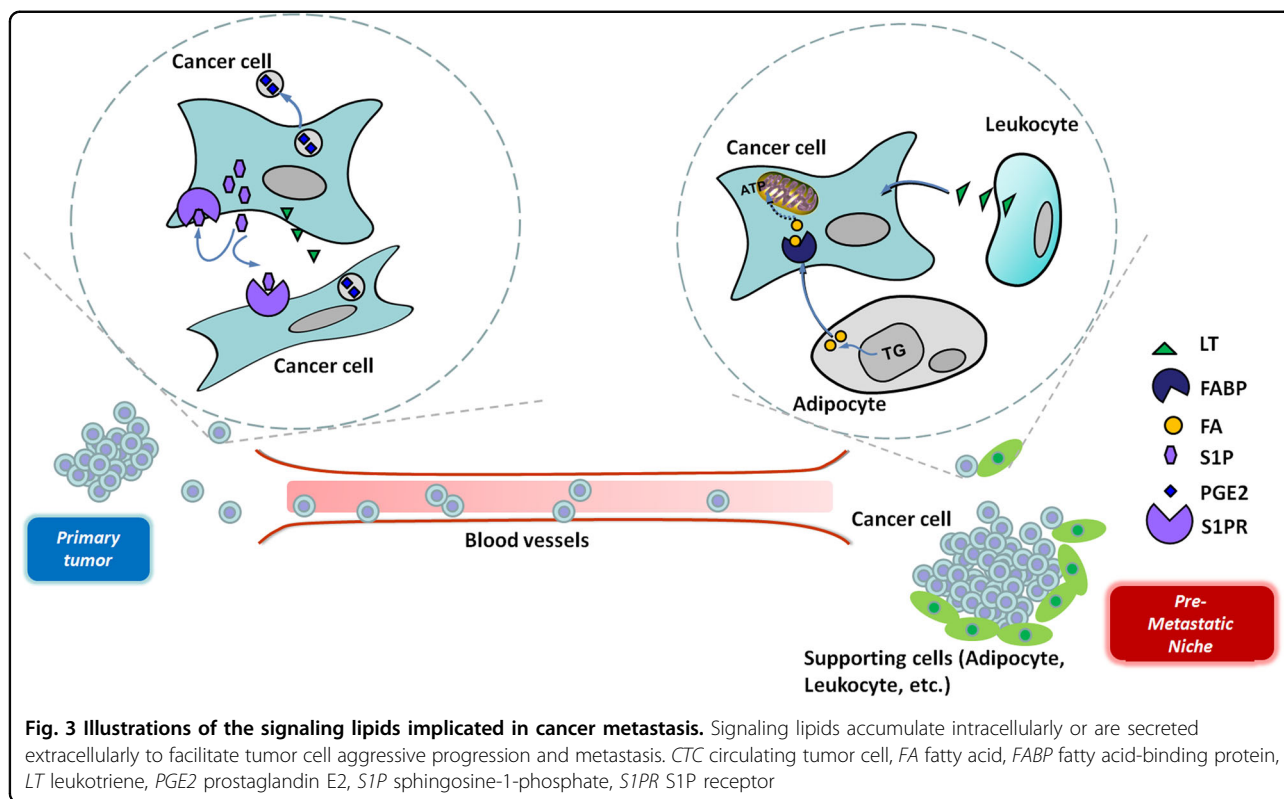
The diverse contents of exosomes, such as nucleic acids, proteins and lipids, makes them an excellent source of noninvasive biomarkers^{112–114}. Some research groups

have exerted efforts to utilize lipids in urine as cancer biomarkers¹¹⁵. A study of urinary carcinoma using exosomal lipidomics revealed differences in the composition of lipid species between the carcinoma and healthy groups¹¹⁵. In addition, the effects of exosomes are not only mediated by their protein and nucleic acid cargo, but, remarkably, exosomal lipids also contribute to their bioactivity. Lombardo's group created synthetic exosome-like lipid raft-rich nanoparticles (SELNs) that were devoid of nucleic acids and proteins¹¹⁶. In pancreatic cancer cells, SELNs activated the NF- κ B/SDF-1 α axis and promoted the binding of secreted SDF-1 α to chemokine receptors (CXCR4) on the cell surface to further drive the Akt survival pathway¹¹⁶. Thus, exosomal lipids may enhance tumor aggressiveness, metastatic progression and drug resistance.

Altogether, lipids and lipid-metabolizing enzymes may modulate the formation and secretion of exosomes, as well as their bioactivity, and represent potential biomarkers in clinical cancer diagnosis and prognosis.

Conclusions and perspectives

Cancer can be characterized by the malignant and systematic dysfunction of metabolic processes. Metastasis is the most malignant stage of cancer, and lipid reprogramming may contribute to each step of metastatic formation (Fig. 3). In primary cancer cells driven by



oncogenic pathways or restrained microenvironments, the lipid metabolic network is deregulated, and the balance of lipid uptake/mobilization is disrupted. Consequently, the accumulated signaling lipids may mediate intercellular communication between cancerous and noncancerous cells in the tumor microenvironment, thus facilitating the cancer cell EMT program, supporting the maintenance of the CSC subpool, and increasing the number of CTCs, leading to the acquisition of a metastatic phenotype. Moreover, lipid metabolic enzymes and signaling lipids play important roles in the regulation of exosome formation and release from cancer cells. Exosomal lipids can modulate their bioactivity in the tumor microenvironment and during distant dissemination. Furthermore, in premetastatic niches, proinflammatory signaling lipids may help establish microenvironments favorable for cancer metastasis.

Massive medicinal chemistry efforts have sought methods for the chemical modulation of lipid metabolic network nodes critical to pathological processes (Table 1). Moreover, blocking noncancerous cells in microenvironments, such as neutrophil recruitment to premetastatic sites, or decreasing proinflammatory signaling lipid levels may provide novel strategies to abrogate cancer metastatic progression. By considering exosomes as biological drug carriers that could exert specific effects on tumor environments and spreading, an understanding of how their lipid components contribute to exosomal bioactivity in recipient cells will facilitate the design of efficient exosome-based cancer therapeutics. In addition, the development of multimodal imaging CARS microscopy and CARS intravital flow cytometry may support the further elucidation of the mechanistic link between lipid-rich tumors and aggressive tumor behaviors and provide a promising modality for the label-free detection of early-stage cancer metastasis.

Given the complexity of metabolic disorders in cancer, the development of robust portfolios to target oncogenic lipids via integration of multiple chemical modulations, as well as molecular imaging modalities, should offer promising strategies for cancer therapy.

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X.L. was the major contributor to writing the manuscript. X.Z., C.C., and N.L. prepared the original draft. N.L. and Y.L. made the visuals. X.L. and C.C. acquired financial support for the project leading to this publication. Y.C. reviewed and edited the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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